Invasive Bacterial and Fungal Infections Among Hospitalized HIV-Infected and HIV-Uninfected Adults and Adolescents in Northern Tanzania

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(See the editorial commentary by Levine and Farag, on pages 349–351.)

Background. Few studies describe patterns of human immunodeficiency virus (HIV) co-infections in African hospitals in the antiretroviral therapy (ART) era.

Methods. We enrolled consecutive admitted patients aged ⩾13 years with oral temperature of ⩾38.0°C during 1 year in Moshi, Tanzania. A standardized clinical history and physical examination was done and hospital outcome recorded. HIV antibody testing, aerobic and mycobacterial blood cultures, and malaria film were performed. HIV-infected patients also received serum cryptococcal antigen testing and $CD4^+$ T lymphocyte count (CD4 cell count).

Results. Of 403 patients enrolled, the median age was 38 years (range, 14–96 years), 217 (53.8%) were female, and 157 (39.0%) were HIV-infected. Of HIV-infected patients, the median CD4 cell count was 98 cells/μL (range, 1–1,105 cells/ μL), 20 (12.7%) were receiving ART, and 29 (18.5%) were receiving trimethoprim-sulfamethoxazole prophylaxis. There were 112 (27.7%) patients who had evidence of invasive disease, including 26 (23.2%) with *Salmonella* serotype Typhi infection, 24 (21.4%) with *Streptococcus pneumoniae* infection, 17 (15.2%) with *Cryptococcus neoformans* infection, 12 (10.7%) with *Mycobacterium tuberculosis* complex infection, 8 (7.1%) with *Plasmodium falciparum* infection, and 7 (6.3%) with *Escherichia coli* infection. HIV infection was associated with *M. tuberculosis* and *C. neoformans* bloodstream infection but not with *E. coli, S. pneumoniae,* or *P. falciparum* infection. HIV infection appeared to be protective against *Salmonella*. Typhi bloodstream infection (odds ratio, .12; $P = .001$).

Conclusions. While *Salmonella* Typhi and *S. pneumoniae* were the most common causes of invasive infection overall, *M. tuberculosis* and *C. neoformans* were the leading causes of bloodstream infection among HIV-infected inpatients in Tanzania in the ART era. We demonstrate a protective effect of HIV against *Salmonella.* Typhi bloodstream infection in this setting. HIV co-infections continue to account for a large proportion of febrile admissions in Tanzania.

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Fever is a common symptom among patients presenting for hospitalization in Sub-Saharan Africa [1]. While malaria is often perceived to be a leading cause of fever, the importance of community-acquired bloodstream infections due to bacteria, mycobacteria, and fungi is increasingly appreciated [2]. The epidemiology of febrile illness varies geographically. The pattern of etiologies of fever can also be anticipated to change over time with, for example, efforts to control and effectively treat malaria [3], the emergence of the human immunodeficiency virus (HIV) infection pandemic and the increasing availability

of free antiretroviral therapy (ART) [4], introduction of vaccines for *Haemophilus influenzae* type b [5] and *Streptococcus pneumoniae* [6], and changes in environmental risk factors.

Making an etiologic diagnosis in the febrile patient clinically is difficult, and clinical laboratory capacity is often limited in Sub-Saharan Africa [7, 8]. While the capacity to prepare and examine malaria films is widespread, the quality of such examinations may be poor [9], and facilities for blood culture are often absent. Consequently, sentinel hospital bloodstream infection studies using sound methods have provided valuable information to inform empiric treatment guidelines and to help direct disease control efforts [2, 7, 10–15]. In order to understand the role of community-acquired bloodstream infections as causes of febrile illness among adults and adolescents in an area of low malaria transmission intensity during a period of increasing availability of free ART, we studied admissions to 2 hospitals in northern Tanzania.

MATERIALS AND METHODS

Setting

Moshi (population, >144 000) is the administrative center of the Kilimanjaro Region (population, >1.4 million) in northern Tanzania and is situated at an elevation of ~890 m above mean sea level. The climate is characterized by a long rainy period (March–May) and a short rainy period (October–December) [16]. Malaria transmission intensity is low [17]. Kilimanjaro Christian Medical Centre (KCMC) is a consultant referral hospital with 458 inpatient beds serving several regions in northern Tanzania, and Mawenzi Regional Hospital (MRH), with 300 beds, is the regional hospital for Kilimanjaro. Together KCMC and MRH serve as the main providers of hospital care in the Moshi area. In 2008, KCMC admitted 22 099 patients and MRH admitted 21 763 patients.

Participants

Participants were prospectively identified from among adult and adolescent inpatients at the KCMC and MRH in Moshi, Tanzania, from 17 September 2007 through 31 August 2008. All admitted patients aged ⩾13 years and with oral temperatures of ⩾38.0°C were invited to participate in the study. A standardized clinical history and physical examination were performed on consenting patients by a trained clinical officer who was a member of the study team. Provisional diagnoses by the hospital clinical team were recorded and coded using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. Following cleansing of the skin with isopropyl alcohol and povidone iodine, blood was drawn for aerobic blood culture (5 mL) and for mycobacterial blood culture (5 mL) as well as for complete blood count, examination for blood parasites, and HIV antibody testing. The case definition for attribution of febrile illness to malaria was a blood film with ⩾500 asexual parasites per microliter [18]. Acute serum, plasma, and whole blood were archived on all participants. For patients found to be HIV seropositive, $CD4^+$ T lymphocyte count (CD4 cell count) and serum cryptococcal antigen level were also measured. HIV-seronegative patients were screened for the presence of acute HIV infection by polymerase chain reaction (PCR) for HIV-1 RNA. Urine was collected as soon as possible after admission for detection of urine antimicrobial activity and for antigen detection for *Histoplasma capsulatum, S. pneumoniae*, and *Legionella pneumophila* serogroup 1. A chest radiograph was ordered for all patients and was reported using a standardized form by a radiologist (H.C.D.). A discharge form was completed at the time of discharge from the hospital that captured whether the patient died in hospital, the in-hospital management, and the discharge diagnoses coded using ICD-10 codes. The results of all study investigations were provided immediately to the hospital clinical team to inform patient management.

Laboratory Methods

Complete blood count and differential was performed using the CellDyn 3500 automated hematology analyzer (Abbott Laboratories). Thick and thin blood films stained with Giemsa were examined for blood parasites by oil immersion microscopy. Parasite density was determined by standard methods [19].

Blood culture bottles were assessed for volume adequacy by comparing the weight before and after inoculation with blood. Adequate volume was defined as the recommended volume ±20%. BacT/ALERT standard aerobic and mycobacterial bottles were loaded into the BacT/ALERT 3D Microbial Detection system (BioMérieux), where they were incubated for 5 and 42 days, respectively. Standard methods were used for identifying bloodstream isolates. *S. pneumoniae* were serotyped by latex agglutination and the Quellung reaction. Nontyphoidal *Salmonella* were serotyped according to the Kauffmann-White scheme [20]. Antimicrobial susceptibility testing was done according to the methods guidelines of the Clinical Laboratory Standards Institute (Wayne, PA), M100-S18, January 2008 [21].

HIV-1 antibody testing was done on whole blood using both the Capillus HIV-1/HIV-2 (Trinity Biotech) and Determine HIV-1/HIV-2 (Abbott Laboratories) rapid HIV antibody tests. The Capillus test was replaced with the SD Bioline HIV-1/HIV-2 test (version 3.0; Standard Diagnostics) on 4 March 2008 after a change in Tanzania Ministry of Health HIV testing guidelines. If rapid tests were discordant, the sample was tested using enzyme-linked immunosorbent assay (ELISA; Vironostika Uni-Form II plus O Ab; bioMérieux). If the ELISA was negative, no further testing was done. If the ELISA was positive, a Western blot (Genetic Systems HIV-1 Western blot kit; Bio-Rad) was done to confirm the result [22]. HIV-1 RNA PCR was done using the Abbott m2000 system RealTime HIV-1 assay (Abbott

Laboratories) [23]. The CD4 cell count was measured using the FACSCalibur system (Becton Dickinson). Cryptococcal antigen level was measured using the Latex Cryptococcal Antigen Detection System assay (Immuno-Mycologics).

Urine was tested for *S. pneumoniae* and *L. pneumophila* serogroup 1 antigen using the Binax NOW *S. pneumoniae* antigen test and the Binax NOW *Legionella* urinary antigen test (Binax). Urine was tested for *H. capsulatum* antigen using the MVista *H. capsulatum* quantitative antigen enzyme immunoassay (Miravista Diagnostics) [24]. Antimicrobial activity in urine was measured using a modification of the method described by Liu and others [25].

During the study, the laboratory participated successfully in relevant external quality assurance programs of the College of American Pathologists, the Viral Quality Assurance program of the AIDS Clinical Trials Group, and the United Kingdom National External Quality Assessment Service.

Statistical Analysis

Data were entered using the Cardiff Teleform system (Cardiff) into an Access database (Microsoft). For continuous responses, analysis of variance was used to assess treatment differences between groups. For categorical data and binary responses, the Cochran-Mantel-Haenszel test was performed to compare groups. Descriptive statistics for demographics and baseline patient characteristics were obtained for baseline comparability. A multivariate logistic regression analysis was performed to identify risk factors associated with various invasive infections. Backward stepwise logistic regression analysis was conducted for establishing a predictive model of various invasive infections with the selected relevant predictors. All statistical tests performed were 2-sided at the 5% level of significance. Statistical analyses were performed with SPSS software (version 12.0; SPSS).

Research Ethics

This study was approved by the KCMC Research Ethics Committee, the Tanzania National Institutes for Medical Research National Research Ethics Coordinating Committee, and an institutional review board of Duke University Medical Center.

RESULTS

Over the study period 6353 patients admitted to the medical services of KCMC and MRH were screened for eligibility. Of these, 666 (10.5%) met eligibility criteria and 403 (60.5%) could be enrolled into the study. The median age of study participants was 38 years (range, 14–96 years), and 217 (53.8%) were female. Of 403 standard aerobic and 326 mycobacterial blood culture bottles, 372 (92.3%) and 224 (68.7%) were classified as adequately filled, respectively. Of enrolled patients, 112 (27.7%) had evidence of an invasive bacterial or fungal infection, 68 (16.6%) on the basis of a clinically important organism isolated from blood culture. Twenty-nine (4.0%) of the blood cultures were contaminated. Eight (2.0%) participants had malaria parasites present on blood film; all were identified as *Plasmodium falciparum* and the median density of asexual forms was 46800 parasites/μL (range, 174–113880 parasites/μL). Of patients with *P. falciparum*, infection, 6 (75.0%) had ⩾500 parasites/μL. One hundred fifty-seven (39.0%) of the participants were HIV seropositive, including 62 (39.5%) with no prior history of a positive HIV test, and 1 (.2%) participant was HIV seronegative but had an HIV-1 RNA load of >10000000 copies/mL, which is consistent with acute HIV infection. Of HIV-infected patients, the median CD4 cell count was 98 cells/μL (range, 1–1,105 cells/μL), 96 (61.1%) had CD4 cell counts of <200 cells/μL, 29 (18.5%) were taking trimethoprim-sulfamethoxazole (SXT) prophylaxis, and 20 (12.7%) were receiving ART. Two hundred fifty-four (63.0%) of 403 patients received provisional diagnoses of malaria.

Relationship Between HIV and Invasive Infections

The relationship between invasive disease and HIV infection is shown in Table 1, and the leading causes of invasive infection are shown in Table 2. Neither of the HIV-infected patients who had *Salmonella* Typhi bacteremia were receiving SXT prophylaxis and their CD4 cell counts were 182 and 94 cells/μL. Of 7 *S. pneumoniae* bloodstream isolates, 1 (14.3%) belonged to serotype 1, 2 (28.6%) to serotype 13, 2 (28.6%) to serotype 19A, 1 (14.3%) to serotype 19F, and 1 (14.3%) to serotype 46. Of 2 nontyphoidal *Salmonella* bloodstream isolates, both were serotype Typhimurium. Of 7 *S. pneumoniae* isolates, 7 (100%) were susceptible to chloramphenicol, 6 (85.7%) were susceptible to erythromycin, and the remainder were resistant; 5 (71.4%) were susceptible to penicillin and the remainder showed intermediate susceptibility; and 3 (42.9%) were susceptible to SXT and the remainder were resistant. Of 28 *Salmonella enterica* isolates, 3 (10.7%) were susceptible to ampicillin and the remainder were resistant; 28 (100%) were susceptible to ceftriaxone; 20 (71.4%) were susceptible to chloramphenicol and the remainder were resistant; and 28 (100%) were susceptible to ciprofloxacin, and none showed decreased ciprofloxacin susceptibility [26].

Antimicrobial Use Prior to Admission

Among those whose urine was tested, 87 (22.3%) demonstrated urine antimicrobial activity. Of 294 blood cultures drawn from patients without demonstrated urine antimicrobial activity, 51 (17.3%) were positive; whereas of 79 blood cultures drawn from patients with urine antimicrobial activity, 19 (24.1%) were positive (odds ratio, 1.51 [95% confidence interval, .83–2.74]; $P = .175$).

Predictors of Invasive Disease

Risk factors for predicting invasive disease were identified by multivariable logistic regression analysis and are displayed in Table 3.

Table 1. Invasive Infections Among HIV-Infected and HIV-Uninfected Participants, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2007–2008

Pathogen	No. (%) of participants			OR (95% CI)
	All (*n*=403)	HIV-infected (*n*=161)	HIV-uninfected (*n*=244)	
Enterobacteriaceae				
Escherichia coli	7 (1.7)	3 (1.9)	4 (1.6)	1.14 (.25–5.16)
Enterobacter cloacae	1 (.3)	0 (.0)	1 (.4)	[a]
Klebsiella species	1 (.3)	0 (.0)	1 (.4)	[a]
Klebsiella pneumoniae	1 (.3)	1 (.6)	0 (.0)	[a]
Morganella morganii	1 (.3)	1 (.6)	0 (.0)	[a]
Salmonella serotype Typhi	26 (6.4)	2 (1.2)	24 (9.8)	.12 (.03–.49)
Nontyphoidal *Salmonella*	2 (.5)	2 (1.2)	0 (.0)	[a]
Other gram-negative organisms				
Legionella pneumophila serogroup 1[b]	0 (.0)	0 (.0)	0 (.0)	[a]
Neisseria species	1 (.3)	1 (.6)	0 (.0)	[a]
Pseudomonas aeruginosa	1 (.3)	0 (.0)	1 (.4)	[a]
Gram-positive organisms				
Staphylococcus aureus	3 (.7)	1 (.6)	2 (.8)	.76 (.07–8.41)
Streptococcus pneumoniae[c]	24 (5.9)	14 (10.9)	10 (4.1)	2.04 (.96–5.15)
Streptococcus pyogenes	1 (.3)	1 (.6)	0 (.0)	[a]
Yeasts				
Cryptococcus neoformans[d]	17 (4.2)	17 (10.6)	0 (.0)	Undefined
Histoplasma capsulatum[e]	4 (1.0)	3 (2.4)	1 (.4)	4.61 (.48–44.75)
Mycobacteria				
Mycobacterium sherrisii	1 (.3)	1 (.6)	0 (.0)	[a]
Mycobacterium simiae	1 (.3)	1 (.6)	0 (.0)	[a]
Mycobacterium tuberculosis	12 (3.0)	12 (7.5)	0 (.0)	Undefined
Plasmodia				
Plasmodium falciparum	8 (2.0)	1 (.6)	7 (2.9)	.21 (.03–1.74)
Other *Plasmodium* species	0 (.0)	0 (.0)	0 (.00)	[a]
Total no. of participants with invasive infections[f]	112 (27.7)	61 (37.9)	51 (20.9)	2.31 (1.48–3.60)

[a] Numbers are too small to calculate a test statistic.

[b] By urine antigen testing.

[c] Of invasive *S. pneumoniae* infection diagnoses, 7 were by blood culture and the remainder were by urine antigen detected with negative blood culture.

[d] Of invasive *C. neoformans* infection diagnoses, 6 were by blood culture and the remainder were by serum antigen detection with negative blood culture.

[e] All *H. capsulatum* infection diagnoses were by urine antigen detection.

[f] Three patients had 2 organisms isolated from their blood and 1 patient had 3 organisms isolated.

In-Hospital Case Fatality

The hospital outcome was known for 398 (98.8%) participants of whom 41 (10.3%) died. Those who died in hospital included 2 (18.2%) with *M. tuberculosis* bloodstream infection, 5 (31.3%) with *C. neoformans* infection, 2 (7.4%) with *S. pneumoniae* infection, and 12 (10.9%) with any invasive infection. There were no deaths associated with histoplasmosis, typhoid fever, or malaria. Eleven (9.9%) participants with invasive infection died in hospital, whereas 30 (10.3%) without invasive infection died ($P = .736$). Thirty (19.7%) HIV-infected participants died in hospital, whereas 11 (4.8%) of the HIV-uninfected participants died ($P < .001$).

DISCUSSION

We demonstrate that invasive bacterial and fungal disease and HIV infection are common among febrile adult and adolescent inpatients in Moshi, Tanzania, and that the majority of these patients received a provisional diagnosis of malaria. *Salmonella*. Typhi and *S. pneumoniae* are the leading causes of bloodstream infection in this setting. HIV-associated *M. tuberculosis* bacteremia and *C. neoformans* invasive disease are important causes of febrile illness and death, even 3 years after the availability of free ART.

While *Salmonella enterica* is known to be a leading cause of community-acquired bloodstream infection in Sub-Saharan

Table 2. Leading Organisms Identified by Blood Culture and Antigen Detection Among 112 Participants With Invasive Infections, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2007–2008

Pathogen	No. (%) identified by blood culture or antigen detection
Salmonella serotype Typhi	26 (23.2)
Streptococcus pneumoniae[a]	24 (21.4)
Cryptococcus neoformans[b]	17 (15.2)
Mycobacterium tuberculosis	12 (10.7)
Plasmodium falciparum	8 (7.1)
Escherichia coli	7 (6.3)
Others	18 (16.1%)

[a] Of invasive *S. pneumoniae* diagnoses, 7 were by blood culture and the remainder were by urine antigen detected with negative blood culture.

[b] Of invasive *C. neoformans* diagnoses, 6 were by blood culture and the remainder were by serum antigen detection with negative blood culture.

Africa, nontyphoidal *Salmonella* serotypes usually predominate and *Salmonella*. Typhi has been uncommon [2, 27]. Malaria has been associated with risk for invasive nontyphoidal *Salmonella* infection in Africa; it is possible that the low prevalence of malaria in Moshi may be linked to the uncommon occurrence of invasive nontyphoidal *Salmonella* infection [28]. The high prevalence of both typhoid fever and HIV infection in this study allowed us to examine the relationship between HIV infection and typhoid fever. Our study showed an apparent protective effect of HIV against *Salmonella*. Typhi bacteremia—an effect that has also been observed in a meta-analysis of studies of community-acquired bloodstream infection in Sub-Saharan Africa [2]. It is possible that this finding is a result of a patient selection effect resulting from studying patients at the hospital rather than the community level [29]. Alternatively, HIV may modify the risk of the host for *Salmonella*. Typhi infection or disease directly through changes in the gut mucosa or through modification of the host immune response. HIV-infected persons may use SXT prophylaxis which in turn could protect against typhoid fever, although the low prevalence of use of SXT prophylaxis among HIV-infected persons enrolled in this study makes this explanation less likely.

HIV infection was common among study participants, who frequently presented with immunologically advanced HIV disease. HIV-associated *M. tuberculosis* bacteremia and *C. neoformans* invasive disease were common and were associated with high in-hospital case fatality rates. The predominance of *M. tuberculosis* and *C. neoformans* 3 years after free ART became available in the catchment area of the study hospitals is striking and is not dissimilar to the results of a study completed a decade earlier elsewhere in Tanzania, long before the advent of ART programs [12]. These findings underscore the importance of promoting HIV counseling and testing services [30, 31], improving access of persons with HIV to care and treatment [32], and, while such programs are expanded, continuing to provide adequate support to services for the management of opportunistic infections. Acute HIV infection was identified as the likely cause of febrile illness in $<1\%$ of participants in our study, which confirms that the diagnosis is rare but warrants consideration in this setting. However, the prevalence of acute HIV infection was much lower than that observed among febrile outpatients in Uganda [33]. The lower prevalence of acute HIV infection in our study could be due to geographic differences in HIV epidemiology or to the fact that patients with acute HIV infection may be more likely to seek outpatient care than to be hospitalized.

As anticipated for an area of low malaria transmission intensity [17], malaria was a relatively uncommon cause of fever in this study. Despite malaria being uncommon, the majority of study participants received a provisional diagnosis of malaria, which is consistent with other studies [34]. This finding illustrates the importance of improving clinician awareness of bacterial and fungal bloodstream infections and broadening empiric treatment strategies to include bacterial pathogens. Antimicrobial susceptibility testing of common bacterial pathogens in this study demonstrates a high prevalence of resistance to ampicillin and SXT and the presence of chloramphenicol resistance. Third-generation cephalosporins provide good coverage for common bacterial pathogens, and fluoroquinolones remain active for *S. enterica*. Pre-hospital use of antibacterial and antimalarial drugs, confirmed by detection of urine antimicrobial activity, was common in this study. Exposure to antimicrobial agents prior to hospital admission was not associated with decreased or increased risk for bloodstream infection. However, it is likely that the frequent pre-hospital use of antimicrobials would lead to differences in the spectrum of pathogens observed at the hospital compared with the community level [29].

While distinguishing the various causes of febrile illness clinically is problematic, we did identify a number of clinical or simple laboratory tests that can aid in diagnosis in this setting. HIV antibody testing can be of great value in identifying a group at high risk for *C. neoformans* and *M. tuberculosis* infection. A history of headache and weight loss and a positive Kernig sign are useful for identifying those with cryptococcal disease; chronic cough and lymphadenopathy were associated with disseminated tuberculosis. A history of dyspnea, elevated white cell count, and hypotension were associated with pneumococcal disease, whereas patients with typhoid fever tended to be younger and have a higher magnitude of fever, a history of rigors, and diarrhea.

Among patients with invasive disease, most deaths were recorded in those with *M. tuberculosis*, *C. neoformans*, and *S. pneumoniae* disease. No in-hospital deaths occurred in those with histoplasmosis, typhoid fever, or malaria. While HIV-infected patients were more likely to die during hospitalization

Table 3. Predictors of Invasive Infections Among All Study Participants, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2007–2008

Infection	Finding	Odds Ratio	*P*
Cryptococcus neoformans	Kernig sign	6.96	.049
	Headache	4.81	.039
	Weight loss	3.56	.040
	Past HIV infection diagnosis	3.25	.069
	Lymphocyte count per 1 cell/μL	1.04	.007
	Platelet count per 1 cell/μL	1.01	.004
	Male sex	.21	.013
	Infiltrate on chest radiograph	.18	.029
	Fever per 1°C	.04	.015
Histoplasma capsulatum	Skin lesions	13.07	.054
	Oxygen saturation per 1%	.81	.002
Mycobacterium tuberculosis	Past HIV infection diagnosis	20.64	.008
	Chronic cough	7.54	.013
	Lymphadenopathy	5.88	.048
	Heart rate per 1 beat/min	1.05	.017
	Lymphocyte count per 1 cell/μL	.87	.006
	Hematocrit level per 1%	.49	.004
	Dyspnea	.05	.007
Streptococcus pneumoniae	Dyspnea	4.53	<.001
	White blood cell count per 1 cell/μL	1.16	.006
	Lymphocyte count per 1 cell/μL	1.04	.049
	Systolic blood pressure per 1 mm Hg	.96	.020
	Chronic fever	.28	.044
Salmonella serotype Typhi	Rigors	3.86	.084
	Diarrhea	3.03	.026
	Fever per 1°C	1.43	.011
	Age per 1 year	.95	.011
	Crepitations on chest auscultation	.20	.018
Any invasive infection	Normal breath sounds on chest auscultation	2.12	.004
	Fever per 1°C	1.80	.001
	Weight loss	1.69	.050
	Lymphocyte count per 1 cell/μL	1.22	<.001
	Neutrophil count per 1 cell/μL	1.16	.001
	Diastolic blood pressure per 1 mm Hg	.98	.020
	Oxygen saturation per 1%	.93	.007
	Hematocrit level per 1%	.54	.010

than those without HIV, there was no difference in risk for in-hospital death between those with and those without bloodstream infection. It is likely that the diagnostic services provided to clinicians through this study facilitated the targeting of antimicrobial therapy and may have improved patient outcomes. However, it is notable that 10% of febrile patients without a diagnosed invasive infection died in hospital. This finding suggests that further work to explore additional etiologies of fever is warranted.

This study had a number of limitations. Bias may have been introduced due to failure to enroll all eligible patients. Furthermore, the study duration of only 1 year did not allow us to assess changes across longer periods.

In summary, we demonstrate that invasive bacterial and fungal diseases are common causes of febrile illness among hospitalized patients in northern Tanzania. Although free ART had been available in the hospital catchment area for 3 years at the time of the study, many febrile patients had HIV infection with immunologically advanced HIV disease. HIV-associated disseminated tuberculosis and cryptococcal disease were common and associated with high inpatient case fatality rates. The high prevalence of typhoid fever in the study area provided a rare opportunity to study its epidemiologic interaction with HIV. HIV infection appeared to provide a protective effect against *Salmonella*. Typhi bacteremia—a finding that warrants further study. Many patients received a provisional diagnosis of

malaria, although malaria was uncommon. Improved clinician awareness of invasive bacterial and fungal disease, strengthened clinical microbiology services, and use of empiric treatment directed at causes of fever other than malaria may improve patient outcomes. Since antimicrobial resistance to amplicillin, SXT, and, to a lesser extent, chloramphenicol is common, third-generation cephalosporins and fluororquinolones may be useful agents for empiric management of bacterial sepsis. We identified a number of clinical features that may help to identify patients with any invasive infection and those with specific infections. The fact that 10% of patients with febrile illness and no etiologic diagnosis died in hospital suggests that etiologies of fever other than those examined in this study may contribute to patient outcomes and should be the subject of future research.

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